Metabolic Transcriptional Effectors in Heart Disease

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DISCLOSURE INFORMATION:
D. Kelly serves on Scientific Advisory Boards for Lilly, Phrixus, and Johnson & Johnson.
Energy Metabolic Programming in the Developing and Diseased Heart

Physiologic growth and metabolic maturation

Fetal Heart → Postnatal Heart

Glucose
Lactate

Mitochondrial number/function & redistribution;

Adult Heart → Failing Heart

Fatty acids
Glucose

Mitochondrial functional capacity

Fatty acids
Glucose

ATP

Pathologic hypertrophy (HTN, Ischemia)
PPARγ Coactivator-1α (PGC-1α): Inducible, Cardiac-enriched Transcriptional Coactivator

adapted from Soyal et al., Diabetologia 2006
Energy Metabolic Programming in the Developing and Diseased Heart

Fetal Heart
- Glucose
- Lactate

Postnatal Heart
- Mitochondrial number/function & redistribution;

Adult Heart
- Fatty acids
- Glucose

Failing Heart
- Fatty acids
- Glucose

PGC-1α

ATP
Probing the PGC-1α Transcriptional Regulatory Cascade Using Gene Targeting in Mice

-lof studies

PGC-1α

MEF-2

NRF-1

NRF-2

? Sarcomere Metabolism

MtDNA Replication Electron Transport OXPHOS

Estrogen-related Receptor α (ERRα) Null-Heart Failure Following TAC

Huss et al, Cell Metab, 2007

Mitochondrial Fatty Acid β-Oxidation
The PGC-1 Transcriptional Coactivator Family

**PGC-1α**

- NRs
- NRF-1
- MEF-2
- FOXO1

- **activation**
- **Proline-rich**
- **Leucine-rich**
- **RNA recognition and splicing**

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**Loss-of-function studies in mice**

- **PGC-1α**
  - Minimal Cardiac Phenotype
  - Pathologic remodeling following TAC
  - (Arany et al, PNAS, 2006)

- **PGC-1β**
  - Minimal Cardiac Phenotype

- **PRC**
  - ??
Conclusions: Generalized Combined PGC-1α/β Loss-of-function


PGC-1α and PGC-1β:

- Are required for the perinatal

What is the function of PGC coactivators in the adult??

- Dispensable for fetal survival and early stage formation of mitochondria

- Significant functional and target gene overlap, at least in heart
Combined PGC-1α/PGC-1β KO in Fast Skeletal Muscle (MLC-2f-Cre) Results In Profound Exercise Intolerance

Low Intensity Protocol: 1h @ 10 m/min then 2 m/min increment every 15 min; no incline

*, p < 0.05 vs. βflox; #, p < 0.05 vs. β−/−; $, p < 0.05 vs. α−/−
Combined Loss of PGC-1α and β in Skeletal Muscle Reduces Oxidative Capacity but not Oxidative (1 or 2a) Fibers

**SDH**

- αβ+/+
- α−/−
- β−/−
- αβ−/−

**ATPase (Type 1)**

- αβ+/+
- α−/−
- β−/−
- αβ−/−

**Immuno MHC**

- αβ+/+
- α−/−
- β−/−
- αβ−/−
Mitochondrial Structural Abnormalities in Muscle of skPGC-1α/β-/- Mice

**WT (cre-, αwt, βf/f)**

**βKO (MLCcre+, αwt, βf/f)**

**αβ KO (MLCcre+, ako, βf/f)**
Acute Cardiac-specific PGC-1β Gene Disruption on Chronic PGC-1α-/- Background Causes Severe HF

M-mode Echocardiography

LV Fractional Shortening
Lack of Cardiac Dysfunction in MHC-MerCre Hearts following Two-dose (50mg/kg) Tamoxifen Regimen

**Time point:**
2 days after 2nd TAM dose
Mitochondrial Structural Abnormalities Following Disruption of PGC-1β gene in PGC-1α/- Background

Control  α/-β^{f/f}

α/-βcs/-MerCre
Charcot-Marie-Tooth Disease: Mitochondrial Derangements Due to Mutations in the Mitofusin (Mfn) 2 Gene

Brain (2006), 129, 2093–2102
Mechanisms of Mitochondrial Fission and Fusion

Reduced Cardiac mtDNA Levels and Mfn Gene Expression in PGC-\(\alpha/\beta\)-deficient Heart

- mtDNA levels are significantly lower in \(\alpha^{-/-}\beta^{f/f}\) compared to \(\alpha^{-/-}\beta^{f/f/cre}\) with a reduction of 31.4%.

- Mfn1 and Mfn2 gene expression is significantly increased in \(\alpha^{-/-}\beta^{f/f}\) compared to \(\alpha^{-/-}\beta^{f/f/cre}\).

- Drp-1 and Fis-1 gene expression remains relatively unchanged between the two groups.
Conclusions: PGC-1 Signaling in Adult Striated Muscle

- The control of mitochondrial integrity in striated muscle is remarkable dynamic and requires PGC-1-mediated transcriptional control.

- In states of PGC-1 deficiency, loss of mitochondrial quality control may contribute to pathologic remodeling in heart and skeletal muscle (and brain?)

IS THE PGC-1 CASCADE A RATIONALE THERAPEUTIC TARGET FOR HEART FAILURE AND OTHER DISEASES THAT REDUCE MITOCHONDRIAL FUNCTIONAL RESERVE?
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